Changes in coagulation in standard laboratory tests and ROTEM in trauma patients between on-scene and arrival in the emergency department

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Abstract: BACKGROUND: When trauma patients arrive in the emergency department (ED), coagulopathy frequently is present. The time course, however, in which this coagulopathy develops is poorly understood. No study has fully evaluated the coagulation status, including thromboelastometry on-scene and at hospital arrival. We hypothesized that measured coagulation variables might change when measured at the scene of injury and upon arrival to the ED. METHODS: We performed a prospective, single-center, observational study investigating coagulation status in 50 trauma patients on-scene and at arrival in the ED. Measurements included arterial blood gases, ROTEM®, protein S100, protein C activity, protein S, Quick value, international normalized ratio, activated partial thromboplastin time, D-dimer, coagulation factor V (FV), coagulation factor XIII (FXIII), fibrinogen, hemoglobin, hematocrit, platelets, and volume and blood products being administered during the first 24 hours. RESULTS: Significant changes between on-scene and the ED were observed for the following values: partial venous oxygen pressure increased and sodium, glucose, and lactate decreased. For EXTEM, INTEM, and APTEM, clotting time and clot formation time increased significantly, whereas maximal clot firmness and angle decreased significantly (all P 0.004). For FIBTEM, clotting time increased significantly and maximal clot firmness decreased significantly. In the laboratory, significant reductions in hemoglobin, hematocrit, platelets, activated partial thromboplastin time, fibrinogen, FV, FXIII, protein C activity, protein S, and protein S100 were observed (all P 0.001). CONCLUSIONS: Although most all laboratory and rotational thromboelastometry coagulation tests worsened over time when measured on-scene and in the ED, monitoring coagulation at the scene of trauma does not provide clinically important information in a majority of trauma patients. One hour after injury, significant activation and consumption of fibrinogen, FV, FXIII, protein C activity, and protein S were observed.

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Changes in Coagulation in Standard Laboratory Tests and ROTEM in Trauma Patients Between On-Scene and Arrival in the Emergency Department

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BACKGROUND: When trauma patients arrive in the emergency department (ED), coagulopathy frequently is present. The time course, however, in which this coagulopathy develops is poorly understood. No study has fully evaluated the coagulation status, including thromboelastometry on-scene and at hospital arrival. We hypothesized that measured coagulation variables might change when measured at the scene of injury and upon arrival to the ED.

METHODS: We performed a prospective, single-center, observational study investigating coagulation status in 50 trauma patients on-scene and at arrival in the ED. Measurements included arterial blood gases, ROTEM® , protein S100, protein C activity, protein S, Quick value, international normalized ratio, activated partial thromboplastin time, D-dimer, coagulation factor V (FV), coagulation factor XIII (FXIII), fibrinogen, hemoglobin, hematocrit, platelets, and volume and blood products being administered during the first 24 hours.

RESULTS: Significant changes between on-scene and the ED were observed for the following values: partial venous oxygen pressure increased and sodium, glucose, and lactate decreased. For EXTEM, INTEM, and APTEM, clotting time and clot formation time increased significantly, whereas maximal clot firmness and angle α decreased significantly (all $P \leq 0.004$). For FIBTEM, clotting time increased significantly and maximal clot firmness decreased significantly. In the laboratory, significant reductions in hemoglobin, hematocrit, platelets, activated partial thromboplastin time, fibrinogen, FV, FXIII, protein C activity, protein S, and protein S100 were observed (all $P \leq 0.001$).

CONCLUSIONS: Although most all laboratory and rotational thromboelastometry coagulation tests worsened over time when measured on-scene and in the ED, monitoring coagulation at the scene of trauma does not provide clinically important information in a majority of trauma patients. One hour after injury, significant activation and consumption of fibrinogen, FV, FXIII, protein C activity, and protein S were observed. (Anesth Analg 2014;XXX:00–00)

Although considerable progress has been made in trauma resuscitation, traumatic hemorrhage and coagulopathy remain major causes of mortality.[1,2] Morbidity and mortality in patients with trauma-induced coagulopathy is up to 4 times greater than in patients without trauma-induced coagulopathy.[3] The so-called "lethal triad" of coagulopathy, acidosis, and hypothermia starts early after traumatic injury and is associated with increased mortality.[4–6] In addition, hemodilution, shock with hypoperfusion of tissues, and inflammation also may play a role.[7–9] As a result of these early derangements, one-third of patients arriving in the emergency department (ED) present with coagulopathy.[10–12]

The identification and the early treatment or avoidance of coagulopathy are thus of major interest and should be initiated in the prehospital setting because the mean time from injury to arrival in the ED has been described in the literature as approximately 75 minutes in Europe and North America, which exceeds the "golden hour."[11–13] Although Floccard et al.[14] studied conventional variables of coagulation at the trauma scene, no comprehensive study on conventional, plasma-based coagulation variables, including coagulation factor XIII (FXIII) and whole blood coagulation measures such as rotational thromboelastometry (ROTEM® delta; TEM® International GmbH, Munich, Germany), has been performed. In this study, we investigated the initial changes and the course of conventional, plasma-based coagulation variables, including FXIII, ROTEM, variables of blood gas analysis, protein S, and protein C activity, from on-scene to the ED in traumatized patients with an NACA score ≥III. (NACA score is a scoring system of the severity in cases of medical emergencies such as injuries, diseases, or poisonings. It was developed from the National Advisory Committee for Aeronautics for accidents in aviation.)

METHODS

The protocol was approved by the local ethics committee (Kantonale Ethikkommission Zurich, Switzerland, study number StV 21–2008) including the fact that subjects were exempted from consent because the first blood sample was drawn under conditions in which patients could not give informed consent.[15] Patients or their relatives (in case of

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death) were contacted once they were medically stabilized to get delayed consent. If consent was refused, the patient and all data were removed from the study.

This single-center, prospective, observational study was conducted from April 2009 to October 2012 at the University Hospital Zurich in collaboration with the emergency medical services (EMS) of the city of Zurich, Switzerland (Schutz und Rettung Stadt Zürich).

To be eligible for this study, patients had to be older than 18 years of age, sustain blunt or penetrating trauma, have an NACA score of ≥III, and the time between trauma and the first blood sample had to be <30 minutes. An NACA score of III indicates a moderate-to-severe but not life-threatening disorder that requires stationary treatment and often emergency medical measures on-scene (e.g., femur fracture, mild stroke, smoke inhalation). An NACA score of IV is a serious event in which rapid development of a life-threatening condition cannot be excluded and emergency medical care is required. Exclusion criteria were cardiopulmonary resuscitation, death on site or during transportation, and administration of any type of colloid or >500 mL of crystalloids before the first blood sample was drawn.

On-scene, a first IV line was placed not to delay treatment of the patient. A second IV line was placed on the other side of the body to draw blood samples for the study. To avoid interference attributable to stasis, samples were drawn in the following sequence: (1) 9-mL serum blood (S-Monovette®; SARSTEDT AG & Co., Nümbrecht, Germany), (2) 9-mL EDTA blood (EDTA K_3, S-Monovette; SARSTEDT AG & Co.), (3) 10-mL citrated blood (1 mL 3.2% trisodium citrate + 9 mL blood, S-Monovette; SARSTEDT AG & Co.), and (4) 1 blood gas analysis syringe (arterial blood gas sampler 1 × 1.7 mL, 80 IU heparin, SafePICO aspirator; Radiometer Medical, Bronshoj, Denmark).

The same blood samples were drawn once the patient arrived in the ED of the University Hospital in Zurich, Switzerland. Blood samples from both collection periods were then analyzed. Several studies have demonstrated that blood samples remain stable during a long period of time at 21°C, and the analysis results are not distorted.[16,17] For ROTEM analyses, samples are considered stable for up to 120 minutes.[18] Blood gas analyses were performed using multiwavelength hemoximetry (ABL 800; Radiometer Medical A/S, Bronshoj, Denmark). For both samples, pH, hematocrit (Hct), hemoglobin (Hb), lactate, glucose, base excess (BE), partial venous oxygen tension (pvo_2), partial pressure of carbon dioxide (pvco2), potassium, sodium, ionized calcium, chloride, and bicarbonate were measured.

The ROTEM device analyzes the kinetics and quality of clot formation and clot lysis in whole blood and in real time. The following tests were performed: INTEM (ellagic acid–activated intrinsic pathway), EXTEM (tissue factor–triggered extrinsic pathway), FIBTEM (with platelet inhibitor cytochalasin D, evaluating the contribution of fibrinogen to clot formation), and APTEM (inhibition of plasmin to evaluate hyperfibrinolysis).

The following variables were determined: clotting time (CT), clot formation time (CFT), maximal clot firmness (MCF), maximal lysis (ML), and alpha-angle (α).

Two identical rotational thromboelastometry devices were used, equipped with 4 channels each. Both devices underwent complete technical revision by the manufacturer before starting the study. Tests ran for exactly 62 minutes. Further technical details of ROTEM coagulation analysis have been published previously by Theusinger et al.[18]

In the central laboratory, the following variables were determined for the 2 time points: Hb, Hct, erythrocytes, leukocytes, platelets, Quick test, international normalized ratio (INR), activated partial thromboplastin time (aPTT), fibrinogen, protein S100, protein S activity, protein C activity, D-dimers, coagulation factor V (FV), and coagulation factor XIII (FXIII) activity. All measurements were performed by a quality-controlled International Organization for Standardization (ISO) 17025–accredited institutional laboratory using the manufacturer's reagents and according to the manufacturer's instructions. Hb, Hct, platelet count, erythrocytes, and leukocytes were analyzed with the Sysmex XE-5000 (Sysmex Digitana, Horgen, Switzerland). Assessment of INR was determined by the Behring Coagulation System (BCS) XP (Siemens Healthcare Diagnostics GmbH, Eschborn, Germany) via use of the Innovin® test. aPTT was measured by BCS XP with the Actin® FS test. Fibrinogen (Clauss method) was measured by BCS XP by the use of Multifibrin U®. FXIII activity was determined by BCS XP. Protein C activity was measured using the protein C chromo on BCS XP. This kit measures how much protein C activity can be activated by snake venom extract (snake venom derivative of the Southern Copperhead, *Agkistrodon contortrix*, Protac®; Sekisui Diagnostics, LLC, Stamford, CT). Protein S was determined by using the Innovance® Free protein S. All aforementioned kits are manufactured by Siemens Healthcare Diagnostics GmbH, Eschborn, Germany. D-dimers were determined using the mini VIDAS® D-Dimer Exclusion (bioMerieux, Lyon, France) test. Protein S100 was determined by the hospital ISO 17025–accredited chemical laboratory using chemical additives and Cobas® 8000 automatic analyzing system by Roche Diagnostics GmbH (Mannheim, Germany).

Other data collected at the scene and after arrival in the ED, were as follows: time from injury until arrival in the ED, age, sex, anatomic-based injury location, injury severity score (ISS), systolic, diastolic, and mean arterial blood pressures, heart rate, transfusion requirements during the first 24 hours after administration to the hospital, type and volume of fluids administered, use of coagulation factors, and 30-day mortality. Preexisting diseases or treatments were not documented.

Polytrauma was defined as either monotrauma, multitrauma, or polytrauma according to Butcher and Balogh.[19] Monotrauma was defined as an injury to 1 body region and was considered severe if ISS >15 or ISS <15 with significant physiological deterioration. Multitrauma was defined as having >1 body region injured but with an abbreviated injury scale not exceeding 3 in 2 regions and without the presence of systemic inflammatory response syndrome. Polytrauma injury required at least 2 body regions with an abbreviated injury scale >3 and with the presence of systemic inflammatory response syndrome on at least 1 day during the first 72 hours. Severity of traumatic brain injury (TBI) was defined via the Glasgow Coma Scale.

The colloid used by the EMS of Zurich was 6% hydroxyethyl starch (HES, Tetraspan® HES 130/0.42; B. Braun AG, Melsungen, Germany). In the ED of the University Hospital

Zurich, HES 4% gelatin (Physiogel®; B. Braun AG) also was used. The crystalloid used by the EMS and the University Hospital Zurich was a balanced lactated Ringer's solution (Ringerfundin®; B. Braun AG).

Blood product usage was guided by our institutional blood transfusion algorithm. According to this guideline, the transfusion trigger for red blood cells (RBCs) was Hct >21%,[20] fibrinogen was administered if the patient was bleeding and the FIBTEM showed an MCF <7 mm, FXIII was given when the laboratory result was <60% or when 6 g of fibrinogen had been given, and prothrombin complex concentrate (PCC) was administered according to the Quick value.

Statistical Analyses

Floccard et al.[14] presented medians and interquartile ranges of changes in coagulation between on-scene and the ED. We included INR, aPTT, fibrinogen, and FV into sample-size considerations. The SDs of changes were obtained as interquartile range/1.35. We found that FV needed the largest sample size. A sample size of 44 patients will have a power of 90% to detect a mean change of 0.1 IU/mL when the SD of changes is 0.2 IU/mL, using a paired *t* test with a 5% 2-sided significance level. We thus enrolled 50 patients in this study.

Data were analyzed using Microsoft® Excel (Microsoft Office 2010; Microsoft Corporation, Redmond, WA) and IBM® SPSS® Statistics version 20 (SPSS Inc., Chicago, IL). Continuous variables were summarized as mean ± SD and if necessary presented as median [minimum; maximum]. Continuous and count data were compared between on-scene and after arrival in the ED using the Wilcoxon signed rank test. Ninety-five percent confidence intervals (CIs) of mean changes were computed based on the central-limit theorem. The ISS and Quick value were correlated with laboratory and blood gas results using Spearman rank test and reporting the correlation coefficients. Incidences of pathologic laboratory parameters were compared using the McNemar test. To address multiple comparisons, *P* values of ≤0.01 were considered significant.

RESULTS

Patient Characteristics

Fifty patients were included in this study. Six patients (12%) died during the first 30 days. The mean age was 44 ± 21 years, and 37 patients (74%) were male. The mean body weight was 73 ± 14 kg, height 173 ± 7 cm, and body mass index 24.4 ± 4.1. All patients experienced blunt trauma. Fourteen patients (28%) were classified as monotrauma, 19 patients (38%) as multitrauma, and 17 patients (34%) as polytrauma. Forty-four patients sustained a TBI (18 mild, 10 moderate, and 16 severe). In 14 (82%) of the polytrauma patients, a TBI was part of the injury (Table 1). The mean ISS on arrival at the ED was 25 ± 22 with a median [minimum; maximum] value of 17 [4; 75]. The time from injury to arrival in the ED was 50 ± 16 (45[23; 83]) minutes. On-scene, systolic, diastolic, and mean arterial blood pressures were 127 ± 30, 80 ± 14, and 95 ± 18 mm Hg, respectively. Heart rate on-scene was 85 ± 21 beats per minute and stayed the same until arrival in the ED (88 ± 28 beats per minute). In the ED, systolic blood pressure was 126 ± 28 mm Hg, diastolic was lower (72 ± 18 mm Hg), and mean arterial blood pressure was significantly lower compared with on-scene with 90 ± 20 mm Hg ($P < 0.001$), respectively (Table 2).

Volume Management

In all patients, blood samples were drawn before any colloid and <500 mL crystalloids were given. Until arrival in the ED, all 50 patients received crystalloids, and 8 patients received HES as well. On average, patients received 542 ± 432 mL of crystalloids and 79 ± 222 mL of colloids between on-scene and arrival in the ED and before the second blood sample was drawn in the ED. In the ED and during the first 24 hours of hospitalization, 48 patients received crystalloids and 19 patients additionally received colloids (Table 2). More fluids were given in the ED (1076 ± 1294 mL [$P = 0.007$]

Table 1. Patient Characteristics and Injury Data

Characteristics	All patients (*n* = 50)
Age, y	44 ± 21 (42 [17; 94])
Male sex	37 (74%)
BMI, kg/m²	24.4 ± 4.1 (23.0 [19.2; 35.5])
Injury	
Monotrauma/multitrauma/ polytrauma	19/14/17
Monotrauma with TBI	17
Multitrauma with TBI	13
Polytrauma with TBI	14
TBI	44 (88%)
TBI (mild/moderate/severe)	18/10/16
ISS	25 ± 22 (17 [4; 75])
ISS ≥16	29 (58%)
ISS = 75	6 (12%)
Time from on-scene to ED; min	50 ± 16 (45 [23; 83])

Values are expressed as mean ± SD (median [minimum; maximum]) or number (%).

BMI = body mass index; TBI = traumatic brain injury; ISS = injury severity score; on-scene = period from injury to arrival at the emergency department; ED = emergency department.

Table 2. Procedural Data On-Scene and After Arrival ED

Characteristics values	On-scene (*n*)	ED + first 24 hours (*n*)	*P*
BPsyst, mm Hg	127 ± 30	126 ± 28	0.30
BPdiast, mm Hg	80 ± 14	72 ± 17	0.012
MAP, mm Hg	95 ± 18	90 ± 20	≤0.001
Heart rate, bpm	85 ± 21	88 ± 28	0.76
Crystalloids[a], mL	542 ± 432 (50)	1076 ± 1294 (48)	0.007
Colloids[a], mL	79 ± 222 (8)	454 ± 995 (19)	≤0.001
RBC, units	0	17 ± 8 (3)	
FFP, units	0	9 ± 2 (2)	
Platelets, units	0	3 ± 2 (3)	
Tranexamic acid, g	0	1.2 ± 0.4 (8)	
PCC, IU	0	2000 ± 817 (3)	
Fibrinogen, g	0	8.9 ± 4.8 (7)	
Factor XIII, IU	0	2813 ± 2049 (4)	

Values are expressed as mean ± SD and *n* (number of patients treated), volumes infused refer between on-scene and arrival in the ED.

ED = emergency department; BPsyst = systolic blood pressure; BPdiast = diastolic blood pressure; MAP = mean arterial blood pressure; bpm = beats per minute; RBC = red blood cell; FFP = fresh-frozen plasma; PCC = human prothrombin complex, which includes factor II, VII, IX, X, activated protein C, and protein S; IU = international unit; on-scene = period from injury to arrival at the emergency department.

[a]Administered after on-scene blood sample withdrawn.

crystalloids and 454 ± 985 mL [$P < 0.001$] colloids) than during the period between on-scene and arrival in the ED.

Blood Products

No blood products or coagulation factors were administered between the scene of injury and arrival in the ED (Table 2). In the ED, RBCs, fresh-frozen plasma, and platelets were given in 3 (6%), 2 (4%), and 3 (6%) patients, respectively, after the second blood sample was drawn. Tranexamic acid (Cyklokapron®; Pfizer Corporation Austria GmbH, Vienna, Austria) was administered in 8 patients (16%). Four-factor (II, VII, IX, and X) PCC (Beriplex® P/N; CSL Behring AG, Bern, Switzerland) was given in 3 patients (6%). Seven patients (14%) received fibrinogen (Haemocomplettan®; CSL Behring AG) and in 4 patients (8%), FXIII (Fibrogammin®; CSL Behring AG) was given. Data presented are the mean ± SD of factors or blood products of patients having received any of those products. FXIII was given with a mean of 2813 ± 2049 IU with a range of 1250 to 6250 IU. Fibrinogen 8.9 ± 4.8 g was given with a range of 4 to 18 g. Four-factor PCC was given with a mean of 2000 ± 817 IU with a range of 1000 to 3000 IU. Tranexamic acid was administered with 1.2 ± 0.4 g with a range of 1 to 2 g.

In the first 24 hours (ED, operating room, and intensive care unit), the mean ± SD (range) RBC use was 17 ± 8 (6–26) units, platelet use was 3 ± 2 (1–6) units, and fresh-frozen plasma use was 9 ± 2 (7–11) units.

Blood Gas Analysis

Significant changes (all $P \leq 0.005$) between on-scene and the ED were observed for Pvo_2, sodium, glucose, and lactate. Twenty-four patients had a pH <7.34 on-scene, and in 2 patients, the pH was <7.20. In the ED, a pH <7.34 was measured in 27 patients and a pH <7.20 in 1 patient. Lactate values above the normal upper threshold of 1.6 mmol/L were measured in 45 patients on-scene and in 31 patients in the ED. Lactate values >4 mmol/L were measured in 11 patients on-scene and in 5 patients in the ED. Details are shown in Table 3. The pH ($r = -0.27$; $P = 0.05$, not significant), HCO_3^- ($r = -0.30$; $P = 0.032$, not significant), and BE values ($r = -0.32$; $P = 0.022$, not significant) measured on-scene may have correlated weakly with the ISS, but the correlation increased slightly after arrival in the ED (pH [$r = -0.40$; $P = 0.004$], HCO_3^- [$r = -0.32$; $P = 0.024$, not significant], and BE values [$r = -0.41$; $P = 0.003$]). After arrival, the ED lactate values may have correlated weakly with the ISS ($r = 0.29$; $P = 0.038$, not significant). Whereas a possible weak correlation for pH and lactate was found on-scene ($r = 0.36$; $P = 0.011$, not significant), the correlation was moderate and significant in the ED ($r = 0.58$; $P < 0.001$). Lactate and aPTT did not correlate on-scene ($r = 0.06$; $P = 0.69$, not significant) but may have in the ED ($r = 0.42$; $P < 0.001$); the same results were found for pH and aPTT ($r = 0.05$; $P = 0.72$, not significant on-scene and $r = 0.51$; $P < 0.001$ in the ED).

Laboratory Results

On-Scene

Laboratory values below the lower limit of the normal range were measured for platelets in 3 (6%), fibrinogen in 3 (6%), FV in 2 (4%), FXIII activity in 3 (6%), protein C activity in 5 (10%), and protein S in 6 patients (12%). Thirteen patients (26%) had a Quick value, and 27 (54 %) presented an aPTT below the normal range (Table 4).

Laboratory values above the upper limit of the normal range were measured for platelets in 2 (4%), fibrinogen in 2 (4%), FV in 3 (6%), FXIII activity in 8 (16%), D-dimer >0.5 mg/L in 44 (88%), D-dimer >4 mg/L in 12 (24%), protein C activity in 3 (6%), protein S in 4 (8%), and protein S100 in 49 patients (98%) (Table 4). Quick values, aPTT, fibrinogen, FV, and FXIII activity level did not correlate with the ISS. A significant correlation with ISS was found for Hb ($r = -0.37$; $P = 0.008$), protein S100 ($r = 0.67$; $P < 0.001$), D-dimers ($r = 0.72$; $P < 0.001$), and protein S ($r = -0.41$; $P = 0.003$). Fibrinogen ($r = 0.41$; $P < 0.001$), FV ($r = 0.68$; $P < 0.001$), FXIII activity ($r = 0.41$; $P = 0.003$), protein C activity ($r = 0.45$; $P < 0.001$), and protein S ($r = 0.40$; $P = 0.004$) may have significantly correlated with the Quick value. The only value that may have had weak evidence for a correlation with the aPTT was FV ($r = -0.33$; $P = 0.018$, not significant).

In the ED

The numbers of patients having laboratory values below the lower limit of the normal range increased for platelets in 9 (18%; $P = 0.013$, not significant), fibrinogen in 5 (10%; $P = 0.16$, not significant), protein C activity in 9 (18%; $P = 0.044$, not significant), and protein S in 9 patients (18%; $P = 0.083$, not significant). Quick value and aPTT values

Table 3. Changes of Blood Gas Analysis Data Between On-Scene and After Arrival ED

Characteristics	On-scene (n = 50)	ED (n = 50)	Difference (95% CI)	P
pH	7.32 ± 0.06	7.32 ± 0.08	0.00 (−0.02 to 0.02)	0.98
$Pvco_2$, kPa	6.12 ± 0.95	6.04 ± 1.73	−0.77 (−2.55 to 1.01)	0.15
Pvo_2, kPa	8.80 ± 6.64	17.06 ± 16.30	8.27 (3.71 to 12.83)	0.003
HCO_3, mmol/L	22.94 ± 2.97	22.27 ± 3.46	0.67 (−0.15 to 1.49)	0.052
BE, mmol/L	−2.78 ± 3.26	−3.31 ± 3.96	0.53 (−0.26 to 1.31)	0.21
Anion gap	7.73 ± 3.55	6.97 ± 3.07	0.76 (−0.25 to 1.78)	0.018
K^+, mmol/L	3.87 ± 0.65	3.82 ± 0.56	0.06 (−0.14 to 0.25)	0.82
Na^+, mmol/L	138.28 ± 4.22	137.12 ± 3.89	1.16 (0.37 to 1.95)	0.002
Ca^{++}, mmol/L	1.17 ± 0.08	1.16 ± 0.14	0.01 (−0.03 to 0.04)	0.66
Cl^-, mmol/L	107.44 ± 4.25	107.74 ± 3.58	−0.30 (−1.02 to 0.42)	0.32
Glu, mmol/L	7.63 ± 2.91	7.12 ± 2.64	0.51 (0.10 to 0.92)	0.004
Lct, mmol/L	3.08 ± 1.59	2.29 ± 1.60	0.79 (0.36 to 1.21)	≤0.001

Values are expressed as mean ± SD.

ED = emergency department; CI = confidence interval; $Pvco_2$ = venous carbon dioxide tension; Pvo_2 = venous oxygen tension; HCO_3 = bicarbonate; BE = base excess; K^+ = potassium; Na^+ = sodium; Ca^{++} = calcium; Cl^- = chloride; Glu = glucose; Lct = lactate; on-scene = period from injury to arrival at the emergency department.

Table 4. Pathologic Laboratory Parameters On-Scene and After Arrival in the ED

Characteristics	On-scene (*n*)	ED (*n*)	Total changes, *n* (%), 95% CI	*P*
Hb, <12 g/dL	5	19	14 (28), 17%–42%	<0.001
Hct, <36%	6	24	18 (36), 24%–50%	<0.001
Platelets <143 g/L	3	9	6 (12), 6%–24%	0.014
Leukocytes >9.6 g/L	21	21	14 (28), 17%–42%	1.0
Quick value <70%	13	12	11 (22), 13%–35%	0.76
INR >1.3	2	3	3 (6), 2%–16%	0.564
aPTT				
<26 s	27	18	19 (38), 26%–52%	0.039
>36 s	0	1	3 (6), 2%–16%	0.083
FBG				
<1.5 g/dL	3	5	4 (8), 3%–19%	0.32
>4.0 g/dL	2	1	1 (2), 1%–10%	0.32
FV				
>150%	3	13	10 (20), 11%–33%	0.16
<50%	2	3	1 (2), 0%–10%	0.32
FXIII				
>120%	8	3	5 (10), 4%–21%	0.025
<70%	3	10	7 (14), 7%–26%	0.008
D-dimer				
>0.5	44	44	2 (4), 1%–13%	1.0
>4.0	18	24	8 (16), 8%–29%	0.034
Protein C				
>120%	3	2	1 (2), 0%–10%	0.32
<60%	4	9	7 (14), 7%–26%	0.059
Protein S				
>120%	4	2	4 (8), 3%–19%	0.32
<50%	6	9	7 (14), 7%–26%	0.26
Protein S100	49	50	1 (2), 0%–10%	0.32

Incidences are expressed as numbers, and total changes between both time points (patients who changed from pathologic to normal or from normal to pathological values) are expressed as numbers with percent and 95% Wilson CIs. *P* values correspond to McNemar test between time points. Total changes are means that change in a laboratory parameter in comparison with the measurement on-scene and in the ED. This was considered in both directions. This ensures that pathologic laboratory values measured on-scene can be normalized in the ED and vice versa.

ED = emergency department; on-scene = period from injury to arrival at the emergency department; ; CI = confidence interval; Hb = hemoglobin; Hct = hematocrit; INR = international normalized ratio; aPTT = activated prothrombin time; FBG = fibrinogen; FV = coagulation factor V; FXIII = coagulation factor XIII.

below the lower level of the normal range were found in 12 ($P = 0.32$, not significant) and 18 ($P = 0.013$, not significant) patients, respectively. The number of patients having FXIII activity below the normal range and D-dimer levels >4 mg/L increased to 11 ($P = 0.083$, not significant) and 20 ($P = 0.004$) patients, respectively. For other measured variables, the number of patients having laboratory values above the upper limit of the normal range decreased for fibrinogen to 1 (2%; $P = 0.32$, not significant), protein C activity to 2 (4%; $P = 0.32$, not significant), and protein S to 2 patients (4%; $P = 0.16$, not significant). Protein S100 levels were increased in all patients and did not change.

Table 5 presents the significant changes in coagulation measurements between on-scene and arrival in the ED. D-dimers increased; Hb, Hct, and platelets decreased; and protein C activity, protein S, fibrinogen, FV, and FXIII activity, and protein S100 decreased. There was a trend for an increase of aPTT ($P = 0.04$, not significant). Compared with on-scene, no changes in Quick value, INR, and leukocytes were found (Table 5). The Hb ($r = -053$; $P < 0.001$), Hct ($r = -053$; $P < 0.001$), protein S100 ($r = 0.69$; $P < 0.001$), D-dimer ($r = 0.72$; $P < 0.001$), and protein S ($r = -0.54$; $P < 0.001$) were significantly correlated with the ISS. There may have been a weak correlation of FXIII activity ($r = -0.34$; $P = 0.014$, not significant) with ISS.

The correlations of fibrinogen ($r = 0.51$; $P < 0.001$), FV ($r = 0.79$; $P < 0.001$), FXIII activity ($r = 0.54$; $P < 0.001$), protein C activity ($r = 0.57$; $P < 0.001$), protein S ($r = 0.45$; $P = 0.001$), and the D-dimer ($r = 0.32$; $P = 0.025$, not significant) with the Quick value increased compared with those on-scene. Besides FV ($r = -0.40$; $P = 0.004$), protein C activity ($r = -0.35$; $P = 0.012$, not significant) and protein S ($r = -0.33$; $P = 0.018$, not significant) may have correlated weakly with the aPTT.

ROTEM

Changes in ROTEM variables between on-scene and after arrival the ED are shown in Table 6.

On-Scene

In 4 patients (8%), ROTEM variables (CT, CFT, and MCF) were below the lower limit of the normal range. In 1 patient (patient 25), an MCF above the normal range was measured for FIBTEM of the ROTEM. In 5 patients (10%), ML was >15%. All other ROTEM variables measured on-scene were within the normal range.

In the ED

When compared with on-scene, significantly more patients ($n = 18$, 36%) had ROTEM variables below the lower limit of the normal range ($P = 0.002$). In 1 patient (patient 25), an MCF above the normal range was measured for FIBTEM of the ROTEM. Compared with on-scene, an additional 3 patients (6%) had ML >15% upon arrival to the ED. Table 6 presents the significant changes in ROTEM measurements performed between on-scene and the ED. For EXTEM, INTEM, and APTEM, CT and CFT increased significantly, whereas MCF and angle α decreased significantly. For FIBTEM, CT increased significantly, MCF decreased significantly, and ML was interestingly lower in the ED.

Post hoc analysis revealed that exclusion of 3 patients who needed RBC transfusion did not significantly influence any measured variables (hemodynamics, ISS blood gas analysis, laboratory results, and point-of-care results) either on-scene or after arrival in the ED.

DISCUSSION

The main findings early after injury are (1) Quick values were pathologic in at least 13% of the patients (95% CI, 13%–35%) and aPTT in at least 26% (95% CI, 26%–52%), but only aPTT increased significantly after admission in the ED; (2) D-dimer levels were increased in 88% (44 of 50 patients D-dimer >0.5) of the patients and increased significantly until arrival at the ED; (3) Hb, platelet, fibrinogen, FV and FXIII activity, protein C activity, and protein S100 values were significantly decreased from on-scene to ED arrival (Table 5); (4) ROTEM variables were abnormal in 8% of the patients (reduced MCF) on-scene but in 36% of patients after arrival in the ED; (5) protein S100 levels were increased in 98% of the patients on-scene but decreased significantly until admission in the ED (4.14 ± 1.49 to 2.37 ± 4.66; $P < 0.001$); and (6) on-scene 70% of the patients developed lactate levels above the upper limit of the normal range, and half of these patients presented with lactic acidosis.

Table 5. Changes in Laboratory Parameters Between On-Scene and After Arrival ED

Characteristics	On-scene	ED	Difference (95% CI)	*P*
Hb, g/dL	13.92 ± 1.82	12.27 ± 2.01	1.55 (1.13 to 1.97)	≤0.001
Hct, %	39.91 ± 5.01	35.62 ± 5.47	4.59 (3.34 to 5.84)	≤0.001
Platelets, $\times 10^9$/L	259.26 ± 84.18	213.14 ± 75.18	46.12 (32.43 to 59.82)	≤0.001
Leukocytes, g/L	10.38 ± 4.86	10.43 ± 4.87	−0.05 (−1.11 to 1.02)	0.99
Quick value, %	81.14 ± 17.70	80.62 ± 18.31	0.52 (−3.49 to 4.53)	0.43
INR	1.13 ± 0.17	1.16 ± 0.27	−0.03 (−0.07 to 0.02)	0.45
aPTT, s	26.26 ± 4.09	29.46 ± 16.82	−3.20 (−7.41 to 1.01)	0.041
FBG, g/L	2.53 ± 0.90	2.10 ± 0.74	0.43 (0.29 to 0.56)	≤0.001
FV, %	107.64 ± 32.09	89.88 ± 29.28	17.76 (11.76 to 23.76)	≤0.001
FXIII, %	110.98 ± 24.83	90.54 ± 26.56	20.44 (15.63 to 25.25)	≤0.001
D-dimer, ng/L	4.80 ± 5.44	7.43 ± 8.44	2.63 (1.18 to 4.07)	≤0.001
Protein C activity, %	94.68 ± 23.65	80.30 ± 22.39	14.38 (9.69 to 19.07)	≤0.001
Protein S100, µg/L	4.14 ± 1.49	2.37 ± 4.66	7.80 (3.78 to 11.82)	≤0.001

Values are expressed as mean ± SD.

ED = emergency department; CI = confidence interval; Hb = hemoglobin; Hct = hematocrit; INR = international normalized ratio; aPTT = activated prothrombin time; FBG = fibrinogen; FV = coagulation factor V; FXIII = coagulation factor XIII; on-scene = period from injury to arrival at the emergency department.

Table 6. Changes in ROTEM Parameters Between On-Scene and After Arrival ED

Characteristics	On-scene	ED	Difference (95% CI)	*P*
EXTEM CT, s	61 ± 21	75 ± 28	13.72 (9.05 to 18.39)	≤0.001
CFT, s	124 ± 40	161 ± 104	36.82 (12.11 to 61.53)	≤0.001
MCF, mm	58 ± 7	50 ± 9	7.60 (6.47 to 8.73)	≤0.001
Angle α in, degrees	68 ± 7	59 ± 9	8.90 (7.31 to 10.49)	≤0.001
ML, %	9 ± 20	6 ± 6	3.14 (−1.84 to 8.12)	0.055
INTEM CT, s	137 ± 29	162 ± 41	25.76 (18.32 to 33.20)	≤0.001
CFT, s	97 ± 40	133 ± 101	36.66 (12.11 to 61.21)	≤0.001
MCF, mm	58 ± 9	50 ± 10	7.26 (5.99 to 8.53)	≤0.001
Angle α, degrees	73 ± 5	64 ± 10	9.14 (7.25 to 11.04)	≤0.001
ML, %	8 ± 18	6 ± 6	2.84 (2.25 to 7.93)	0.23
APTEM CT, s	64 ± 16	79 ± 41	15.62 (5.26 to 25.98)	≤0.001
CFT, s	126 ± 43	178 ± 161	51.24 (10.63 to 91.85)	≤0.001
MCF, mm	57 ± 6	50 ± 8	7.46 (6.11 to 8.81)	≤0.001
Angle α, degrees	66 ± 6	57 ± 10	8.96 (7.22 to 10.70)	≤0.001
ML, %	4 ± 3	4 ± 4	−0.70 (−1.60 to 0.20)	0.084
FIBTEM CT, s	127 ± 502	175 ± 560	−48.30 (−122.28 to 25.68)	≤0.001
MCF, mm	14 ± 5	11 ± 5	3.22 (2.72 to 3.73)	≤0.001
ML, %	7 ± 20	6 ± 10	0.25 (−4.39 to 4.88)	0.017

Values are expressed as mean ± SD.

ROTEM = thromboelastometry; ED = emergency department; CI = confidence interval; EXTEM = tissue factor activation; CT = coagulation time (in second); CFT = clot formation time (in seconds); MCF = maximum clot firmness (in millimeter); ML = maximal lysis (in millimeters); INTEM = contact activation; α = alpha angle; APTEM = tissue factor activation combined with aprotinin; FIBTEM = tissue factor activation combined with platelet inhibition; on-scene = period from injury to arrival at the emergency department.

Data describing changes in the coagulation status of patients are sparse in the early period after trauma. Only 1 study has performed standard coagulation tests and measurements of FV, protein C activity, and antithrombin III on-scene and after admission in the ED of the hospital.[14] Floccard et al.[14] found abnormal coagulation in 56% of their patients on-scene and in 60% on hospital admission. The on-scene coagulopathy was spontaneously normalized in 2 patients, whereas others had the same or a poorer coagulopathy status, which are quite similar findings to ours.

In our study, blood samples were taken directly at the location of the injury and as soon as possible after admission to the ED. In addition, we evaluated coagulation by using several approaches: standard and advanced laboratory coagulation tests, ROTEM, blood gas analysis, and protein S100 as a brain trauma marker.

Several studies have shown that systemic hypoperfusion itself plays a central role in the pathogenesis of early traumatic coagulopathy.[21,22] A dose-dependent association between the degree of coagulopathy after admission to the ED measured with the Quick value and aPTT, and the severity of tissue hypoperfusion has been reported.[23,24] White et al.[25] demonstrated in a swine model that traumatic shock itself significantly reduced the fibrinogen concentration and the clot strength as measured by the maximum amplitude of thromboelastography. The high proportion of patients on-scene with metabolic acidosis and lactate concentrations above the upper limit of the normal range in this study supports the suggestion that significant hypoperfusion states are present very early after severe trauma. Nearly half (n = 23; 46%) of these patients initially developed lactic acidosis (pH <7.34, lactate >1.6 mmol/L) as the result of extensive hypoperfusion of tissues. Six of these patients demonstrated a hypocoagulable state (INR >1.2, Quick value <70%). The other 17 patients still had coagulation variables within the normal range. Another 7 patients were hypocoagulable and had high lactate levels with a pH still in the normal range. Even though lactate concentrations decreased after initial intravascular volume resuscitation until reaching the ED, the degree of acidosis remained the

same. A decrease of lactate and remaining acidosis might be explained by only limited volume replacement in the initial period between on-scene and arrival the ED, which is in agreement with previously reported results and recommendations in the latest update of the European trauma treatment guidelines.[11,26,27] Although acidosis itself may affect coagulation, adverse effects of acidosis on extrinsic and intrinsic coagulation pathways and on platelet function are not generally seen until the pH decreases <7.2.[28] In our study, only 2 patients had a pH <7.2 and both died. These patients developed massive hemorrhage due first to the major injury itself and second to the disturbed coagulation system.

At the scene of trauma, we found a Quick value <70% in 26%, a shortened aPTT in 54%, and an increased D-dimer in 88% of patients. In one-quarter of the patients, the D-dimer concentration was >4 mg/L. The combination of normal Quick value, decreased aPTT, and pathologic high levels of D-dimer suggests a massive activation of coagulation factors (hypercoagulable) leading to their consumption and simultaneously to an activated fibrinolytic system early after trauma. ROTEM analysis found an ML >15% in only 8 patients, showing a systemic hyperfibrinolysis, whereas our other results suggest a local hyperfibrinolysis/fibrinolysis that seems to play a role in the early phase of trauma. The shortened aPTT might be explained by a sudden increase of FVIII in the context of a severe trauma.

Floccard et al.[14] reported similar results but used the scoring system proposed by the International Society on Thrombosis and Haemostasis. They reported that 50% of patients on-scene and 60% of the patients after arrival to the ED experienced trauma-associated coagulopathy and that D-dimer levels were increased both on-scene and after admission to the ED. In our investigation, the platelet count, aPTT, fibrinogen, FV, FXIII activity, protein C activity, and protein S on-scene were in the normal range and thus gave no indication of the current coagulation state during trauma-associated bleeding. This observation is in agreement with previous findings that procoagulant coagulation factors are critically reduced in the late stages of blood loss.[29,30] Mittermayr et al.[29] and Innerhofer[30] hypothesized that most factors are needed at low concentrations and short half-life times. These hypotheses, however, are based only on investigating the procoagulant and anticoagulant coagulation factors after admission to the hospital. Interestingly, in our study, fibrinogen, FV, FXIII activity, protein C activity, and protein S all decreased and aPTT increased between on-scene and the ED. The decrease in coagulation factors is unlikely to have been attributable to dilutional coagulopathy because only small volumes of crystalloids (1076 ± 1294 mL) and in particular colloids (454 ± 995 mL) were infused between on-scene and arrival the ED. The use of colloids such as HES further predisposes to a coagulopathy which is difficult to reverse.[31] No or little volume (no colloids) given before the first blood drawn is unlikely to have influenced the results of the measurement of this study because the amount of colloids given was 79 ± 222 mL and the amount of crystalloids 542 ± 432 mL before the second blood drawn in the ED are considered low. One possible explanation is that trauma induces a massive coagulation response, including increased protein C activity, which thus leads to a decrease of fibrinogen, FV, FXIII activity, protein C activity and protein S, and an increased aPTT. Because we measured protein C activity based on the not yet protein C activity, our results presented in Table 4 are correct because less unactivated protein C is available in the late phase of trauma due to earlier activation. Data from the German Trauma Registry of 8724 patients show a clear relationship between early coagulopathy and the volume of fluids administered.[12] The registry reported an incidence of early coagulopathy at >40%/>50% and >70% with fluid volumes of >2000, 3000, and 4000 mL, respectively.[12] In contrast, a retrospective study of 1088 traumatized patients by Brohi et al.[27] demonstrated that the incidence of early coagulopathy was not related to preclinical fluid administration but clearly associated with the severity of injury. This shows that there are actually 2 completely opposite ways to explain coagulopathy in trauma patients.

In addition to standard laboratory evaluation, our study included ROTEM measurements both on-scene and after arrival in the ED. On-scene in 8% of the patients, the MCF of the ROTEM was reduced, presenting reduced clot strength and 10% presented an ML >16%. After arrival in the ED, 36% of the patients had abnormal ROTEM parameters, including increases in CT and CFT of EXTEM, INTEM, and APTEM and decreases in angle α and MCF compared with on-scene values. In addition, FIBTEM CT was prolonged and the MCF reduced. These data suggest an early deficiency or loss of activity of coagulation factors such as fibrinogen, FXIII, and platelets and were supported by simultaneously determined platelet count and changes in FV, FXIII activity, protein C activity, and protein S. Davenport et al.[32] hypothesized that traumatic coagulopathy is characterized by reduction in clot strength and has a specific thromboelastometric signature, which can be diagnosed by the clot amplitude at 5 minutes. Although our study was too small to test this possibility, reduced clot strength was seen in more than one-third of the patients in the ED. Another reason for the development of impaired clot formation measured with ROTEM might be a dilutional coagulopathy caused by intravascular volume resuscitation during patient transport to the ED. In an in vitro study, Haas et al.[33] reported significant worsened clot formation after diluting blood samples by using 60% lactated Ringer's solution. In this investigation, the crystalloid volume replacement was only 542 ± 432 mL, and colloid was only given to 8 patients. We thus believe it unlikely that the worsened coagulation and clot formation were caused by dilution. In cases in which clearly pathological values of ROTEM are identified, early treatment as suggested by the European Trauma Guidelines[26] might be useful, and administration of factor concentrates has been suggested to treat traumatic coagulopathy by Theusinger et al.[20]

Limitations

Some limitation of this study should be noted. The study sample size was small. Hence, subgroup analysis for different ISS classes or for patients with significant hypoperfusion states was not performed because of insufficient power. For ethical reasons, blood samples on-scene and in the ED were always performed without disturbing life-sustaining treatment. Therefore, it cannot be ensured that blood samples were drawn before the first dose of volume replacement. In addition, samples for blood gas analysis were performed from a second venous access site and not cooled on ice during

transportation to the ED. However, several studies have demonstrated that blood samples remain stable over a long period of time at 21°C temperature, so we do not believe these values distort our analysis.[16,17] We also did not measure body temperature of our patients on arrival to the ED. Hypothermia may have also altered our measurement of coagulation status. Blood loss was neither calculated nor was it estimated because the data were not available for the days after trauma. In only 8 patients, ML >15% indicated systemic hyperfibrinolysis. These results might suggest that in an early phase of trauma, hyperfibrinolysis could be a local phenomenon because high D-dimers show the presence of fibrinogen split products.

CONCLUSIONS

In the urban setting with transport times <1 hour, coagulation values measured on arrival to the ED change drastically from those measured at the scene of trauma. On-scene measurements thus do not provide clinically relevant information that leads to an acute specific laboratory variable-based therapeutic intervention in most trauma patients. For 1 hour after injury, significant activation and consumption of fibrinogen, FV, FXIII, protein C activity, and protein S were observed. Markers such as increasing D-dimers indicate a progressive fibrinolysis even if not shown by an increased ML in ROTEM. Routine coagulation tests may not indicate the diagnosis of ongoing coagulopathy. Thromboelastometry promises to be a useful tool for early detection of traumatic coagulopathy.

DISCLOSURES

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Contribution: This author designed the study, conducted the study, analyzed the data, and wrote the manuscript.
Attestation: Oliver M. Theusinger approved the final manuscript.
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REFERENCES

1. Sauaia A, Moore FA, Moore EE, Moser KS, Brennan R, Read RA, Pons PT. Epidemiology of trauma deaths: a reassessment. J Trauma 1995;38:185–93
2. Cothren CC, Moore EE, Hedegaard HB, Meng K. Epidemiology of urban trauma deaths: a comprehensive reassessment 10 years later. World J Surg 2007;31:1507–11
3. Esposito TJ, Sanddal TL, Reynolds SA, Sanddal ND. Effect of a voluntary trauma system on preventable death and inappropriate care in a rural state. J Trauma 2003;54:663–9
4. Cosgriff N, Moore EE, Sauaia A, Kenny-Moynihan M, Burch JM, Galloway B. Predicting life-threatening coagulopathy in the massively transfused trauma patient: hypothermia and acidoses revisited. J Trauma 1997;42:857–61
5. Tieu BH, Holcomb JB, Schreiber MA. Coagulopathy: its pathophysiology and treatment in the injured patient. World J Surg 2007;31:1055–64
6. Theusinger OM, Spahn DR, Ganter MT. Transfusion in trauma: why and how should we change our current practice? Curr Opin Anaesthesiol 2009;22:305–12

7. Eddy VA, Morris JA Jr, Cullinane DC. Hypothermia, coagulopathy, and acidosis. Surg Clin North Am 2000;80:845–54
8. Hess JR, Brohi K, Dutton RP, Hauser CJ, Holcomb JB, Kluger Y, Mackway-Jones K, Parr MJ, Rizoli SB, Yukioka T, Hoyt DB, Bouillon B. The coagulopathy of trauma: a review of mechanisms. J Trauma 2008;65:748–54
9. Theusinger OM, Madjdpour C, Spahn DR. Resuscitation and transfusion management in trauma patients: emerging concepts. Curr Opin Crit Care 2012;18:661–70
10. Brohi K, Cohen MJ, Davenport RA. Acute coagulopathy of trauma: mechanism, identification and effect. Curr Opin Crit Care 2007;13:680–5
11. MacLeod JB, Lynn M, McKenney MG, Cohn SM, Murtha M. Early coagulopathy predicts mortality in trauma. J Trauma 2003;55:39–44
12. Maegele M, Lefering R, Yucel N, Tjardes T, Rixen D, Paffrath T, Simanski C, Neugebauer E, Bouillon B; AG Polytrauma of the German Trauma Society (DGU). Early coagulopathy in multiple injury: an analysis from the German Trauma Registry on 8724 patients. Injury 2007;38:298–304
13. Kaufmann CR, Dwyer KM, Crews JD, Dols SJ, Trask AL. Usefulness of thrombelastography in assessment of trauma patient coagulation. J Trauma 1997;42:716–20
14. Floccard B, Rugeri L, Faure A, Saint Denis M, Boyle EM, Peguet O, Levrat A, Guillaume C, Marcotte G, Vulliez A, Hautin E, David JS, Négrier C, Allaouchiche B. Early coagulopathy in trauma patients: an on-scene and hospital admission study. Injury 2012;43:26–32
15. Wright DW, Clark PL, Pentz RD, Hertzberg V, Kellermann AL. Enrolling subjects by exception from consent versus proxy consent in trauma care research. Ann Emerg Med 2008;51:355–60, 360.e1–3
16. Hankinson SE, London SJ, Chute CG, Barbieri RL, Jones L, Kaplan LA, Sacks FM, Stampfer MJ. Effect of transport conditions on the stability of biochemical markers in blood. Clin Chem 1989;35:2313–6
17. Betsou F, Roussel B, Guillaume N, Lefrère JJ. Long-term stability of coagulation variables: protein S as a biomarker for preanalytical storage-related variations in human plasma. Thromb Haemost 2009;101:1172–5
18. Theusinger OM, Nürnberg J, Asmis LM, Seifert B, Spahn DR. Rotation thromboelastometry (ROTEM) stability and reproducibility over time. Eur J Cardiothorac Surg 2010;37:677–83
19. Butcher N, Balogh ZJ. The definition of polytrauma: the need for international consensus. Injury 2009;40(Suppl 4):S12–22
20. Theusinger OM, Stein P, Spahn DR. Applying 'Patient Blood Management' in the trauma center. Curr Opin Anaesthesiol 2014;27:225–32
21. Abelson AL, O'Toole TE, Johnston A, Respess M, de Laforcade AM. Hypoperfusion and acute traumatic coagulopathy in severely traumatized canine patients. J Vet Emerg Crit Care (San Antonio) 2013;23:395–401
22. White NJ. Mechanisms of trauma-induced coagulopathy. Hematology Am Soc Hematol Educ Program 2013;2013:660–3
23. Brohi K, Cohen MJ, Ganter MT, Matthay MA, Mackersie RC, Pittet JF. Acute traumatic coagulopathy: initiated by hypoperfusion: modulated through the protein C pathway? Ann Surg 2007;245:812–8
24. Niles SE, McLaughlin DF, Perkins JG, Wade CE, Li Y, Spinella PC, Holcomb JB. Increased mortality associated with the early coagulopathy of trauma in combat casualties. J Trauma 2008;64:1459–63
25. White NJ, Martin EJ, Brophy DF, Ward KR. Coagulopathy and traumatic shock: characterizing hemostatic function during the critical period prior to fluid resuscitation. Resuscitation 2010;81:111–6
26. Spahn DR, Bouillon B, Cerny V, Coats TJ, Duranteau J, Fernández-Mondéjar E, Filipescu D, Hunt BJ, Komadina R, Nardi G, Neugebauer E, Ozier Y, Riddez L, Schultz A, Vincent JL, Rossaint R. Management of bleeding and coagulopathy following major trauma: an updated European guideline. Crit Care 2013;17:R76
27. Brohi K, Singh J, Heron M, Coats T. Acute traumatic coagulopathy. J Trauma 2003;54:1127–30
28. Meng ZH, Wolberg AS, Monroe DM III, Hoffman M. The effect of temperature and pH on the activity of factor VIIa: implications for the efficacy of high-dose factor VIIa in hypothermic and acidotic patients. J Trauma 2003;55:886–91
29. Mittermayr M, Streif W, Haas T, Fries D, Velik-Salchner C, Klingler A, Oswald E, Bach C, Schnapka-Koepf M, Innerhofer P. Hemostatic changes after crystalloid or colloid fluid administration during major orthopedic surgery: the role of fibrinogen administration. Anesth Analg 2007;105:905–17
30. Innerhofer P. Perioperative management of coagulation. Hamostaseologie 2006;26:S3–14
31. Kind SL, Spahn-Nett GH, Emmert MY, Eismon J, Seifert B, Spahn DR, Theusinger OM. Is dilutional coagulopathy induced by different colloids reversible by replacement of fibrinogen and factor XIII concentrates? Anesth Analg 2013;117:1063–71
32. Davenport R, Manson J, De'Ath H, Platton S, Coates A, Allard S, Hart D, Pearse R, Pasi KJ, MacCallum P, Stanworth S, Brohi K. Functional definition and characterization of acute traumatic coagulopathy. Crit Care Med 2011;39:2652–8
33. Haas T, Fries D, Velik-Salchner C, Reif C, Klingler A, Innerhofer P. The in vitro effects of fibrinogen concentrate, factor XIII and fresh frozen plasma on impaired clot formation after 60% dilution. Anesth Analg 2008;106:1360–5